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Abstract

Aims and Objectives: To investigate the effects of delivering the 'Sepsis Six' bundle by Critical Care Outreach on patient outcomes.

Background: ~~The~~ 'Sepsis Six' ~~bundle~~, is designed to facilitate early intervention with three diagnostic and three therapeutic steps to be delivered ~~by ward staff~~ within 1 hour ~~to patients with suspected sepsis~~.

Design: In a prospective observational study, all adult patients on the general wards from June 2012 to January 2014 with sepsis screened ~~and treated~~ by the critical care outreach team were included, ~~where 'Sepsis Six' was delivered by trained outreach nurses~~.

Methods: ~~Our m~~ Main outcome measure was the change in National Early Warning Score ~~following the delivery of in response to the~~ 'Sepsis Six' ~~bundle~~ within 24 hours.

Secondary outcomes were 90-day mortality and overall bundle compliance.

Results: 207 patients were included in the analysis. Overall bundle compliance was 84%. National Early Warning Scores decreased significantly after 24 hours of administering the 'Sepsis Six' from 7.4 ± 2.6 to 3.1 ± 2.4 ($p < 0.001$). The distribution of the National Early Warning Score changed significantly. Mortality was lower at 90 days when patients who presented with signs of sepsis within 48hrs of hospital admission were compared with those who presented with signs of sepsis after 48 hours of hospital admission (14.5% vs. 35.4% $p < 0.03$) despite similar baseline physiological variables.

Conclusion: We found better outcomes after the administration of Sepsis Six.

Reliable delivery of the bundle, defined as 80% of patients receiving the standard of care, is achievable and our quality improvement data suggest it is likely to be sustainable in our environment.

Relevance to clinical practice: Sepsis Six can reduce physiological impairment, monitored by the National Early Warning Scores. Consistent delivery of the bundle can lead to better patient outcomes.

Introduction

In the UK, sepsis is estimated to kill 44 000 patients annually, and consume 50% of critical care resources (Vincent *et al.*, 2014). The definition has changed recently, putting emphasis on the dysregulated host response to infection leading to organ failure (Singer *et al.*, 2016). The clinical criteria in this new definition closely mirror the previous “severe sepsis” definition, which has been the cornerstone of several quality improvement initiatives worldwide (Levy *et al.*, 2003; Westphal *et al.*, 2011; Na *et al.*, 2012; Levy *et al.*, 2014). Severe sepsis is often mischaracterized as a diagnosis cared for primarily in the intensive care unit (ICU). Yet studies indicate that only 32% to 50% of patients with severe sepsis require ICU care, leaving the majority on the general care wards (Esteban *et al.*, 2007; Rohde *et al.*, 2013). These studies also reveal mortality rates of 26 – 30% among patients with severe sepsis who are not admitted to an ICU compared to 11–33% in the ICU. Interestingly on the general medical ward renal and cardiac dysfunction were commonly observed organ failures, whereas in the ICU, severe sepsis has been reported to more likely involve respiratory failure (Rohde *et al.*, 2013).

~~Inspired by the Surviving Sepsis Campaigns resuscitation bundle, the~~
~~In the UK~~
~~Daniels et al recently developed an operational solution reflective of NHS practice to~~
~~improve delivery of the bundle (Daniels, 2011; Daniels et al., 2011; Borgert et al.,~~
~~2017). The ‘Sepsis Six’,~~bundle ~~is designed to facilitate early intervention~~
~~outside the~~
~~critical care environment~~ with three
simple ~~diagnostic and three therapeutic steps~~
~~to be delivered by~~ nurses and doctors staff ~~within 1 hour (Table 1) (Daniels, 2011;~~

Daniels *et al.*, 2011). A local audit in our hospital showed that only 34% of the patients admitted to the ICU with the diagnosis of severe sepsis received the complete 'Sepsis six' bundle on the wards and our point-prevalence study identified barriers such as the inability to obtain the necessary equipment in the variety of ward settings (Szakmany *et al.*, 2015).

~~In response to this~~To address these shortcomings, we launched a quality improvement (QI) initiative utilizing our established Critical Care Outreach team (CCOT) to improve the recognition and treatment of severe sepsis on the general wards by using the 'Sepsis Six' bundle aided by Sepsis bags containing all necessary equipment for the delivery of each task.

Methods

Our study was registered as ~~part of a quality improvement-QI~~ program at the Cwm Taf University Health Board and Ethical approval was deemed unnecessary.

Setting and context

~~The Royal Glamorgan Hospital~~The project took place in ~~is~~ a District General Hospital providing acute care services to a catchment population of 154,000 people. The hospital provides all acute services, including a 24/7 Consultant led Emergency Department, a 10-bed critical care unit with approximately 500 admissions per annum, full range of medical and surgical services, with the exception of thoracic, cardiac, neuro and specialized paediatric surgery. High concentrations of social and

economic deprivation within ~~Rhondda Cynon Taff~~the area have resulted in hospital services.

The QI initiative described in this paper attempted to target the two aims of the national Rapid Response to Acute Illness Learning Set (RRAILS) programme, which formed part of the Welsh 1000 lives patient safety and quality improvement campaign (Hancock, 2015): i: Improving reliability of systems for identification, escalation and treatment of sepsis; ii: Demonstrably improving outcomes from sepsis and other causes of acute deterioration.

~~In 2009, with the leadership of three of the authors (AH, JB and TSz) a Critical Care Outreach service was established according to the specifications of the South Wales Critical Care Network, initially during normal working hours, then quickly expanding to 12 hours every day of the week. From 2016 the CCOT cover has been expanded to 24/7 and as such is the exemplar service within the critical care community in Wales.~~

The team has previously implemented significant changes in the smaller critical care setting to reduce the rate of catheter-related bloodstream infections (Hermon *et al.*, 2015). The lessons learnt from the ~~at is QI~~ project were applied to the introduction of 'Sepsis Six' and Sepsis bags. Before the beginning of the QI intervention significant focus on education of ward staff on the acutely deteriorating patients took place. Standardised communications tools, such as Situation Background Assessment Recommendation (SBAR) reporting and defined risk stratification tools based on the NEWS were deployed, as recommended previously (Hoffman *et al.*, 2017).

A multidisciplinary team with physician, advanced practitioner, nursing, managerial and junior doctor representation from the ICU was formed to address the need of systematic response to sepsis. In order to be comprehensive in our approach to an intervention, the team wanted to address both hospital-specific systems factors as well as clinical factors associated with sepsis. Using data from our internal audit program to identify clinical factors related to ICU admission, we identified the lack of compliance with the 'Sepsis Six' recommendations as a modifiable factor.

Choice of solution and implementation

The 'Sepsis Six' bundle and Sepsis bags were introduced prior to data collection in a concentrated education effort delivered by the CCOT to all ward staff and junior doctors working on the medical and surgical wards.

Ward staff were educated on the application of the sepsis screening tool The sepsis screening tool was based on the original SEPSIS-1 definition, using the SIRS criteria and a clinical suspicion of infection (Bone *et al.*, 1992). Nursing and medical staff

The 'Sepsis bags' were distributed to every ward in the hospital together with a robust training program on their use. The bags contain intravenous fluids, giving sets, cannulas, blood gas syringes, blood culture bottles, vacutainers for haematology, biochemistry and lactate, sterile procedure packs to aid aseptic technique and the extract of the local guidance on appropriate antibiotic prescription in severe infections.

Evaluation of the intervention

A standard pro forma was used to collect data on all patients referred to the CCOT.

All patients (>18 years) where clinical suspicion and the use of the sepsis-screening tool indicated the presence of sepsis and triggered the use of 'Sepsis Six' were included in our database from June 2012 to January 2014. Patients had to receive all elements of the 'Sepsis Six' bundle within 1 hour to achieve compliance. Time zero was taken as the point at which severe sepsis was first identified. We identified time zero retrospectively, by checking back through patients' charts and our pathology database.

National Early Warning Scores (NEWS) ~~which is~~ based on simple physiological variables ~~and used in all Welsh hospitals~~ were recorded at time zero and at 24 hours after the intervention (McGinley and Pearse, 2012). Rate of ICU admission, overall length of hospital stay and length of hospital stay attributed to sepsis, incidence and number of organ dysfunctions (determined by >1 on the SOFA score) were also recorded. In all patients 90-day outcome was recorded.

~~A standard pro forma was used to collect data on all patients referred to the CCOT.~~

Data analysis

Data were entered into an Excel spreadsheet on a password-enabled computer. Hospital identifiers were included until discharge. Any ambiguous fields were clarified with the investigating team.

Patients were grouped into cohorts whether or not they had signs of severe sepsis 24 hours before the delivery of the bundle and whether the severe sepsis was likely

to be community acquired (“Early”) or healthcare associated (“Late”).

Data was analysed using SPSS 20.0 using the chi-square test for categorical data and Wilcoxon test and ANOVA for numerical data.

Results:

207 patients were identified over the 18 months period. The demographic characteristics of the patients are shown in Table 1.

The most frequent source of infection in our cohort was respiratory followed by abdominal and urogenital infections (Supplementary Table 1.).

All patients fulfilled the sepsis criteria and 155 patients had severe sepsis with at least one organ dysfunction. In 50% of the cases sepsis was present for more than 24 hours before Critical Care Outreach assessment.

Sepsis Six and NEWS:

Overall compliance with the ‘Sepsis Six’ bundle within 1 hour was 84% (Supplementary Table 2). All patients with newly developed sepsis received all elements of Sepsis Six within 1 hour, however only 72% of the patients had the Sepsis Six completed within 1 hour if there was sign of sepsis in the preceding 24 hours.

After 24 hours of administering the ‘Sepsis Six’ NEWS decreased significantly to from 7.4 ± 2.6 to 3.1 ± 2.4 ($p < 0.01$, Fig 1). The decrease in the NEWS score changed the distribution of the scores significantly, and none of the patients scored over 8 after 24 hours (Supplementary Fig 1).

A similar decrease in the NEWS was observed even if Sepsis Six was delayed.

When the barriers to completing the Sepsis 6 were analysed, it was found that administration of antibiotics within one hour was the main contributing factor to reduced compliance (Supplementary Table 2). While delivering the bundle, 70 (33.8%) patients were maintained on the same antibiotic, 30 (14.5%) had a change in the regime and 65 (31.4%) were started on new antimicrobials, predominantly penicillin-based broad-spectrum antibiotics according to the hospital guidelines. Out of the 187 blood cultures taken, 23 were positive, however only 10 were deemed clinically significant: 4 E. Coli, 3 Klebsiella pneumoniae, 2 MRSA and 1 MSSA.

Outcome:

90-day mortality was 27.6% and no significant difference between the outcome of sepsis or severe sepsis or with increasing number of organ dysfunctions was demonstrated.

35 patients were admitted to the ICU, 34 of them had severe sepsis. Mortality in this group was 14.3% vs. 24.5% amongst patients who were managed on the ward $p=0.26$. 121 patients (78%) with severe sepsis did not require ICU admission and were managed on the ward.

We found a significantly lower mortality at 90 days when comparing patients who presented with signs of sepsis within 48 hours of hospital admission "Early", with those who presented with signs of sepsis after 48 hours of hospital admission "Late", 14.5% vs. 34.5% ($p<0.03$). This difference was not explained by age, NEWS,

C-reactive protein, white cell count or lactate levels on administration of 'Sepsis Six' (all $p > 0.05$).

Hospital length of stay and sepsis related hospital length of stay was significantly shorter in the "Early" group: 11.5 (8-21) vs. 30 (17-54.5) and 11 (7-20) vs. 18 (8-36) days for 'Early' and 'Late' groups respectively, $p < 0.01$.

No significant difference was found in the initial NEWS, the response in the scores or any of the outcomes when comparing patients who had signs of sepsis more than 24 hours before the critical care outreach assessment, with those who developed sepsis within this period.

Discussion

We have shown that the simple intervention of 'Sepsis Six', which can be delivered by Critical Care Outreach nurses can significantly improve patients' outcomes and may reduce need for ICU admission.

Baseline data on compliance with the "Sepsis Six" was 34% on all patients who were admitted to the ICU with sepsis in 2011 (local audit). Unfortunately, there were no reliable estimates of the number of patients on the general wards with sepsis at the start of the study. To date only point prevalence data available in the UK from the general wards is from our group (Szakmany *et al.*, 2015; 2016; 2018). In June 2014 over a 24 hour period we found that out of 86 at risk patients on the wards with NEWS 3 or above, 17 (20%) fulfilled SEPSIS-2 definition. Four of these patients had NEWS 6 or above, which was the local standard trigger for CCOT review and all four

~~were seen and treated by the CCOT service. A further three patients with lower~~

an isolated problem: we found that only 24 out 290 patients who fulfilled the sepsis criteria were seen by CCOT in 2015 and this hasn't improved in 2016 (Szakmany *et al.*, 2016; 2018). ~~Our operational database developed in conjunction with our QI~~ observation period, there were at least three times as many patients with sepsis on the wards, compared to the ones seen by the CCOT.

The acuity of the cohort was high, as NEWS 7 or higher indicates the need for prompt assessment by a clinical team with critical-care competencies and consideration for transfer of the patient to a higher dependency care area (McGinley and Pearse, 2012). Similar NEWS scores were observed in recent US and UK studies, including ours (Corfield *et al.*, 2014; Szakmany *et al.*, 2016; Churpek *et al.*, 2017; Szakmany *et al.*, 2018). Importantly, 91% of the patients appeared to respond favorably to the Sepsis Six and only six patients had an increase in their NEWS within 24 hours of treatment.

These results support previous studies, where similar patterns were observed when management protocols were implemented (Daniels *et al.*, 2011; Westphal *et al.*, 2011; Tipler *et al.*, 2013). The 'Sepsis Six' bundle has been developed as a tool to provide basic diagnostic and therapeutic interventions at the bedside, outside of the highly specialized ICU environment (Daniels, 2011; Daniels *et al.*, 2011; Borgert *et al.*, 2017). Daniels *et al.* reported that delivery of 'Sepsis Six' was associated with better compliance with the Surviving Sepsis Campaign resuscitation bundle and probably better outcomes (Daniels *et al.*, 2011). The Surviving Sepsis Campaign

resuscitation bundle recommends similar interventions in severe sepsis but within 3 hours, whereas we operated in a much tighter timeframe (Dellinger *et al.*, 2013).

In our study, overall compliance with the delivery of the 'Sepsis Six' bundle was high and above the threshold of 80% where reliability can be assumed. This was only possible with the use of 'Sepsis bags', which contained the necessary equipment and consumables to start prompt treatment. Our data provide further evidence that effective implementation of simple, intervention protocols in form of oxygen, fluid and antibiotic administration can have a dramatic influence on physiological outcomes (Westphal *et al.*, 2011; Na *et al.*, 2012; Dellinger *et al.*, 2013).

-When considering the individual components of the Sepsis Six bundle, it becomes clear that lack of antibiotic administration was the main reason for failing to achieve better compliance. This is the only task which needs medical intervention as all other tasks can be completed by the critical care outreach and ward nursing teams (McNulty *et al.*, 2018). This situation has improved during the study period after the publication of the Public Health Wales report on bacteraemias and the recommendation of an updated standardized antibiotic regime in sepsis (Heginbotham *et al.*, 2013).

~~Overall compliance with the delivery of the bundle was high and above the threshold of 80% where reliability can be assumed. We found that more patients with newly developed sepsis received Sepsis Six within 1 hour, compared with those who had signs of sepsis in the previous 24-hour period. The main reason for this was the delayed recognition of sepsis. At the time of the outreach referral and~~

~~intervention, half of our patients had already had signs of sepsis in the preceding 24-hour period. This highlights the ongoing need for education at ward level, as it is possible that many patients could have deteriorated without intervention. During the study period 28 out of the 35 patients (80%) admitted to the ICU had received the full bundle, a remarkable improvement from the previous audit in our institution when only one third of the severe sepsis patients deemed eligible for ICU admission had this simple bundle delivered.~~

In our cohort, the mortality was 27.6%, which is in line with recent major randomized controlled trials, quality improvement projects, large retrospective reviews and also with that reported by Daniels in a similar setting (Westphal *et al.*, 2011; Daniels *et al.*, 2011; Annane *et al.*, 2013; ProCESS Investigators *et al.*, 2014; Kaukonen *et al.*, 2014). It is important to note that there is very little reliable data available on the mortality of sepsis on the general medical wards and to date no study has investigated this in the UK (Esteban *et al.*, 2007; Ghanem-Zoubi *et al.*, 2011; Stiermaier *et al.*, 2013). Stiermaier *et al.* found that the burden of mortality has increased three-fold after 1 year and it is likely that the 90-day mortality observed in this study is also underestimating the true impact of the disease (Stiermaier *et al.*, 2013). Interestingly, our national point-prevalence study found the mortality of severe sepsis to be 34% (Szakmany *et al.*, 2016). In that study, less than 10% of the patients had 'Sepsis Six' delivered (Szakmany *et al.*, 2016). It is an attractive hypothesis that the reliable delivery of the bundle helped to achieve significantly better outcomes in the present report.

We have observed that patients, who developed severe sepsis more than 48 hours after hospital admission, had a significantly worse outcome despite similar baseline physiological variables. This finding is supported by several studies, which indicate that nosocomial infections have a significantly worse outcome as opposed to community acquired infections (Vincent *et al.*, 2009; Pavon *et al.*, 2013; Morgan *et al.*, 2016). One of the possible explanations for this finding is the development of acquired immune paralysis as a response to critical illness (Hotchkiss, Monneret and Payen, 2013a). ~~In a recent investigation it has been which was shown that immunosuppression is to be~~ an independent predictor of mortality on the ICU (Tolsma *et al.*, 2014). We have recently ~~demonstrated shown~~ that immunosuppression can be seen as early as the first 24 hours of critical illness and it has been postulated that this ongoing phenomenon plays a role in delayed recovery and death (Raby *et al.*, 2013; Hotchkiss, Monneret and Payen, 2013b). Whilst we ~~don't have~~ n't got detailed immunological profile on our patients, it is plausible that the "Late" group has been affected by this phenomenon.

Limitations

This observational study has significant limitations due to the inability to control adequately for confounding factors. We are unable to draw any 'cause and effect' conclusions, although the patients did appear to have better outcomes after the administration of 'Sepsis Six'. One of the major limitations is the inability to determine the true "at risk" population for the whole study period. ~~Unfortunately~~

~~we don't have data on this possible comparator cohort, however our group~~
general wards with sepsis at the start of the study. To date only point-prevalence
data available in the UK from the general wards is from our group, suggesting that
sepsis prevalence is between 3.6%-4.2% depending on the definition and clinical
tool used (Szakmany *et al.*, 2015; 2016; 2018). In June 2014 over a 24-hour period
patients with sepsis were seen by CCOT, raising the possibility of selection bias in
our study. Without reliable electronic track-and-trigger systems in the hospitals
capturing the true at-risk population, this selection bias is inevitable. Furthermore,
the validity and reliability of our findings could be questioned as there is lack of data
on ward-based sepsis outcomes and process measures in the UK. Daniels and
colleagues demonstrated 79% compliance with the bundle, when their 500-bed
district general hospital employed "sepsis nurses" to deliver a QI project similar to
ours (Daniels *et al.*, 2011). More recently, Simmonds and colleagues observed an
increased compliance with the 'Sepsis Six' bundle following individualized,
automated feedback of performance (Simmonds *et al.*, 2013). In both of these
studies the number of patients recruited were similar to ours and both observed
almost identical mortality. Together with local audit reports from the Welsh RRAILS
group these provide external validity and reliability to our study.

Conclusions

With any observational study involving care bundles, it is impossible to distinguish whether delivery of the bundles simply reflects a globally higher standard of care or whether the bundles themselves impact on outcome. We can say with certainty that

delivery of care improved during this study and that patients receiving the 'Sepsis Six' were far less likely to need critical care admission. Reliable delivery of the bundle, defined as 80% of patients receiving the standard of care is achievable and our quality improvement data suggest it is likely to be sustainable in our environment. Although our initial results are encouraging greater investment in education of the ward staff, awareness and refinement of process are needed to embed gold- standard sepsis care outside of the ICU.

What is known about this topic:

- Sepsis has high mortality and recognition on the wards is poor
- Few appropriate therapeutic interventions exist outside of critical care
- Sepsis Six has been shown to be effective, but compliance is low

What this paper adds:

- Sepsis Six can be delivered reliably by the Critical Care Outreach team, especially with Sepsis Bags containing all necessary kit
- NEWS scores reduce significantly within 24 hours when the bundle is applied
- This can lead to better outcomes and reduced ICU admissions

Authors contributions

JB: Study design, data collection, interpretation of the results and writing of the manuscript; SW: Data collection, interpretation of the results and writing up of the first draft of the manuscript. AH.: Interpretation of the results, writing of the first

draft of the manuscript. TSz: Study design, data analysis, interpretation of the results and writing of the manuscript.

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Table 1. Baseline characteristics and outcomes of the patients

Male/female ratio (N)	139/68
Age (years)	69 (60-80)
NEWS on presentation	7 (6-10)
Number of organ dysfunctions	Number and percentage of patients
0	35 (18.4%)
1	62 (32.6%)
2	65 (34.2%)
3	21 (11.1%)
4	7 (3.4%)
Sepsis Six delivered within 1 hour N (%)	174 (84.1%)
Signs of sepsis in previous 24 hours N (%)	105 (50.7%)
Admission to hospital	

Elective surgical	29 (14%)
Emergency surgical	58 (28%)
Medical	120 (58%)
24 hour outcome	
Remained on the ward with NEWS<3 N (%)	96 (46.4%)
Remained on the ward with NEWS>3 N (%)	49 (23.7%)
ICU admission with 4 hours N (%)	22 (10.6%)
DNA-CPR N (%)	17 (8.2%)
90-day outcomes	
Hospital length of stay (days)	21 (10-43)
Sepsis related hospital stay (days)	14 (6-29)
Admitted to ICU N (%)	33 (15.9%)

Managed on the ward N (%)	174 (84.1%)
Mortality N (%)	57 (27.5%)

Data are presented as N (%) or Median (IQR). NEWS: National Early Warning Score;

ICU: Intensive Care Unit; DNA-CPR: Do Not Attempt Cardiopulmonary

Resuscitation order

Figure legends

Figure 1. Changes in NEWS score following delivery of 'Sepsis Six'

Data are presented as boxes and whisker plots. The boxes enclose the interquartile range and median (middle line in each box); the whiskers enclose the minimum and maximum. Differences between the assessment points were tested with Wilcoxon test. *, $p < 0.05$; °, outliers; NEWS: National Early Warning Score